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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,712	08/25/2000	Peter Nawroth	8484-075-999	7074

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/423,712	Applicant(s) NAWROTH ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication app ars on th cover sh t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-21 and 23-32* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-17,20,21 and 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment filed July, 2002 has been entered and assigned as Paper #15. Claim 22 has been canceled. Claims 7, 23-27, and 29 have been amended. Claims 18 and 19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 7-17, 20, 21, and 23-32 are under current examination.

Unless otherwise indicated, prior rejections that have been rendered moot in view of amendments will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-12 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been

set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims are directed to a method of modulating blood vessel formation in a subject comprising locally administering a functional tissue factor (TF) or a fragment thereof in the form of an expressible nucleic acid. Given the broadest reasonable interpretation, the term "a functional tissue factor or a fragment thereof" encompasses numerous (a genus of) fragments, which are functional in modulating blood vessel formation. The specification teaches that TF is a membrane glycoprotein which binds the blood clotting factors, and has a molecular weight of 43 to 46 kD, that "a fragment of TF which is capable of forming vessels, in particular for wound healing" may be used in the instant invention (Specification, page 3, lines 1-13). However, the specification fails to teach which of the fragments from a 43-46 kD protein would still have a proper function of the full length TF, what is the core structure(s) related to such function, therefore, the specification fails to provide an adequate description to teach the structures, the identifying characteristics, and the structure-function relationship of the genus of TF fragments, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

In view of the state of the art in protein chemistry, it is probably one of the most unpredictable areas of biotechnology. Although the polynucleotide-coding region determines amino acid sequence of the protein, it is the conformation of three-dimensional structures that allows the protein to function and carry out the messages of the genome. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach certain position in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). In view of such, one cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structure of polypeptides encompassed by these claims and whether they can serve as a functional TF. Moreover, it is unclear exactly what modifications and variations can be tolerated in this protein and still allow proper TF function. Determination of the effects of particular modifications and fragmentations are not predictable until they are actually made and used, hence resulting in a trial and error situation. *Rudinger* (Peptide Hormones 1976; June;pages 1-7) teaches the relationship of sequence components and the peptide hormone function "THE SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6).

An adequate written description for a functional protein requires more than a mere statement that it is part of the invention. It is not sufficient to define the agents solely by its principal biological property, i.e. "capable of forming vessels, in particular

for wound healing", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any fragment with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all fragments that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical and physical properties of a chemical, or the sequences of a protein and nucleic acids, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the genus of functional fragments of TF. Therefore, only the described full-length TF meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 7-12 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

These claims are drawn to using functional fragments of TF, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for the genus of fragments encompassed by the claims. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, the described full length TF alone is insufficient to describe the genus. One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of fragments encompassed by these claims, thus, one would not know how to use the

invention without first carrying out undue experimentation to determine which of the fragments would have the recited function. Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claims 7-17, and 20-32 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record and following.

In paper #15, applicants argue that the instant invention is enabled because the *therapeutic objective of the method is limited to the initiation of a physiological process where the process itself is still functional but the initiation fails/has failed in the particular diseases.* In response, it is noted that the claims are not limited to the initiation of blood vessel formation; the claims recite "modulating blood vessel formation", which embraces up-regulation, down-regulation, and initiation processes, for example. Further, the claims recite numerous diseases, such as human diabetes mellitus, vasculitis, arterial conclusive disease, infected ulcer, Crohn's disease, and ulcerative colitis, they have distinct and complicated etiologies and mechanisms that lead to impaired wound healing, which may not limited to the initiation of blood vessel formation. Thus, it is highly unpredictable whether locally administration of a nucleic acid expressing TF could achieve the goal of therapeutic symptomatic intervention for all the diseases recited. In fact, the coagulant effect of TF may acerbate arterial occlusive disease or thrombosis. Further, as indicated in the previous Office action, TF initiates multiple biological effects, such as blood clotting and vessel coagulating functions. *McDonald et*

al (US 6,120,799) teach the presence of tissue factor in a tissue with blood vessels would result in the formation of blood clots prevent the flow of nutrients and oxygen to the remainder of the vessel, resulting in the death of the vessel and the surrounding tissue (column 22, lines 1-7). From above teachings, locally applied nucleic acids expressing TF may promote the blood vessel formation or promote death of a vessel and surrounding tissue, thus, the outcome of using TF in a patient would be highly unpredictable given the diversified etiology of the diseases and the nature of the TF having such distinct and paradoxical effects.

Applicants further argue that the instant invention is enabled because it uses non-viral vectors and/or limiting the application to one or only a few administrations, however, the claims *do not place any limitation* on the type of vectors used or the times of administration.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement provision set forth under 35 U.S.C. §112, 1st paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 7-10, 13-17, and 20-25 stand rejected under 35 U.S.C. 102(e) as being anticipated by *McDonald et al* (US 6,120,799), for reasons of record and following.

Applicants argue that *McDonald et al* disclose TF in connection with tumor vascularization, and fail to disclose the treatment of normal tissues.

In response, the claims are not drawn to the treatment of normal tissue, nor excluding tumor tissue. Therefore, the rejection still stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-17, and 20-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *McDonald et al* (US 6,120,799) as applied to claims 7-10, 13-17, and 20-25 above, and further in view of *Dubensky, Jr. et al* (J Virology 1996 Jan;70:508-19), for reasons of record and following.

Applicants argue that the objective of the presently claimed invention is targeted induction of vessel formation in normal tissues, which is completely different from the random, untargeted formation of vessels in tumors. In response, the claims are not drawn to targeted vessel formation in normal tissue, nor excluding tumor tissue. The claims embrace any tissue in need, which implies a diseased tissue, and some of the diseases have been clearly spelled out in claims 30-32.

Applicants further argue that *McDonald et al* assume rather than teach that TF expression results in the death of vessels, and fails to address the right conditions where the pro-angiogenic activity of TF is in favor of the pro-coagulant activity. In response, the intended use limitations bears little weight on the determination of novelty of the invention. In this case, the limitation "modulating blood vessel formation" does little in the determination of anticipation for the claimed products. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure (e.g. method steps) is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Therefore, the rejection still stands.

Claims 7-10, 13-17, 20-25, and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *McDonald et al* (US 6,120,799) as applied to claims 7-10, 13-17, and 20-25 above, and further in view of *Sanford et al* (US 5,100,792), for reasons of record and following.

Applicants presented the same argument as to the preceding rejection, thus, for the same reasons, the rejection still stands.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 27, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER